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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,370	10/03/2001	Randall K. Holmes	33,383-00	8568

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,370	HOLMES ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-17,28-37 and 39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3 and 44* is/are allowed.

6)☒ Claim(s) *1-2,~~4~~11,13-17,28,30-37 and 39-43* is/are rejected.

7)☐ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13-17, 28-37,39-44 are pending.
Claims 12, 18-27 and 38 have been canceled; new claim 44 has been added.
Claim 1 and all claims dependent therefrom have been amended; Claims 15 and 16, 29, 41-43, also have been amended.

Allowable Subject Matter

1. Claim 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
2. Claims 3 and 44 define over the prior art of record and are therefore allowed.

Objections/Rejections Withdrawn

3. Claim 3 is no longer objected to, as it has been amended into an independent claim.

Rejections Maintained

4. Claims 1-2, 4, 6-8,11, 13-17, 28, 30,32-34, 37, 39-43 rejected under 35 U.S.C. 102(b) as being anticipated by WO95/17211 (as evidenced by sequence for cholera toxin and E.coli heat labile enterotoxin provided by Zhang et al (1995, page 564, Figure 1)), is maintained for reasons of record and responses to Remarks set forth below.
5. Claims 1, 2, 13 rejected under 35 U.S.C. 102(b) as being anticipated by Glineur et al (1994 is maintained for reasons of record and responses to Remarks set forth below.

Response to Arguments

6. The rejection of claims 1-2, 4, 6-8,11, 13-17, 28, 30,32-34, 37, 39-43 rejected under 35 U.S.C. 102(b) as being anticipated by WO95/17211 (as evidenced by sequence for cholera toxin and E.coli heat labile enterotoxin provided by Zhang et al (1995, page 564, Figure 1)) is traversed on the grounds that:

   a. "the amino acid residues discussed are those of the wild-type CT sequence" and emphasizes that "an amino acid (other than ASP) that replaces the naturally-occurring Glu that occurs at wild-type CT-A subunit position 29-not the 29th amino acid position of any resulting mutant.

7. It is the position of the examiner that WO95/17211 mutated the wild-type CT sequence to obtain the mutated CT sequence which evidences a substitution of a tyrosine at wild-type CT-A subunit position 29, wherein the resultant CT was a mutant CT holotoxin, with a tyrosine at position 29. As all of the claims do not evidence a reference SEQ ID NO, and the broad

recitation of specific positions, (ie amended claim 1: "naturally occurs at position 29"), requires numbering the amino acids from the N-terminal to the C-terminal, wherein WO95's mutant cholera holotoxin evidenced a tyrosine substitution for the native glutamine at position 29th and thus meets the claim limitations of Applicant's invention. The scope of what is now claimed, requires a different amino acid at position 29, than what is found in the wild-type cholera toxin; WO95' discloses this embodiment.

8. The claims require mutant holotoxin to function as an adjuvant; WO95' discloses this characteristic of their resultant mutant cholera holotoxin.

9. The claims require the antigenic composition to induce and enhanced immune response to a second antigen; WO95' discloses this characteristic of their resultant cholera holotoxin and compositions that comprise the same or equivalent antigens.

10. Applicant asserts that WO95/17211 only mutates LT and not CT and that the "amendments clarify that Applicants' mutant CTs contain an amino acid (other than Asp) that replaces the naturally –occurring Glu that occurs at wild-type CT-A subunit position 29-not at the 29th amino acid position of any resultant mutant and asserts that Applicant's claims requires "a substitution which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin, with an amino acid other than aspartic acid.

11. It is the position of the examiner that WO95' mutant cholera toxin has a tyrosine substituted at position 29 based upon the wild type CT-A subunit numbering. WO95' states at page 4, lines 29-30 that "[I]t is accepted in the art that CT and LT are generally interchangeable, showing considerable homology" and the mutations of LT are applicable for CT "see page 7,

lines 25-28 "[t]he mutant comprises one or more amino acid additions, substitutions or deletions in the amino acid sequence of the A subunit of CT or LT which is or are effective to abolish the toxicity of the toxin. Both CT and LT evidence the same arginine at position 7, and upon deletion of this amino acid (see WO95' claims 3-4), the glutamine "Glu", at position 29 of the wild type A subunit would evidence a tyrosine being substituted at the wild type position 29.

12. Applicant states that Zhang does not discuss any substitutions of the amino acid at the wild-type position 29.

13. It is the position of the examiner that Zhang was only cited as **evidence** of what the wild-type sequence for CT is and to show that the upon deletion of the amino acid at position 7 by WO95', an amino acid other than aspartic acid would be present in the wild-type position 29, specifically tyrosine. WO95 inherently anticipates the instantly claimed invention.

14. The rejection of the claims under 35 USC 102(b) is traversed on the ground that Rappuoli does not teach or suggest the motivation to select amino acid position 29 for modification of any of the bacterial toxins.

It is the position of the examiner that Applicant traverses the rejection as if it were made under 35 USC 103, but the rejection was set forth and maintained under 35 USC 102(b) inherency and Zhang et al was only evidence to show the amino acid sequence of cholera toxin. The instantly claimed invention is directed to an antigenic composition that comprises a mutant cholera holotoxin that has an amino acid other than glutamic acid and aspartic acid at wild-type position 29, WO95' discloses a composition that meets the claimed combination of claim

limitations. The mutant cholera holotoxin of the instant claims is not limited to any specific amino acid sequence or size for the A subunit, as long as the amino acid sequence of the holotoxin can be considered to be a mutant cholera holotoxin produced through changing the amino acid at position 29 of the wild-type subunit A, and the resultant mutant cholera holotoxin has the ability to enhance an immune response to second an antigen in a vertebrate host. Clearly WO95' discloses the mutant holotoxin with a mutation in the A subunit to inherently evidence an amino acid substitution at position 29, and said holotoxin has the functional characteristics recited in the instant claims. The product of the prior and what is now claimed have not been distinguished one from the other based upon the recited functional limitations and minimal (not aspartic acid and not glutamic acid at position 29) structural characteristics recited. The rejection is maintained for reasons of record in the Office Action dated October 13, 2004.

15. The rejection of claims 1, 2, 13 rejected under 35 U.S.C. 102(b) as being anticipated by Glineur et al (1994) is traversed on the grounds that the mutation that removes the glutamine is not a substitution of an amino acid at position 29.

16. It is the position of the examiner that through deletion of the glutamine of the wild-type cholera holotoxin, the resultant holotoxin has a substitution of a tyrosine at position 29. While the reference does not discuss the functional characteristics of the resultant mutant holotoxin containing composition together with a second heterologous antigen, specifically recombinantly expressed ampicillin resistance, and is also in association with the Vibrio cholerae 569B-NT host cell expressed antigens, the composition of the prior art and what is now claimed have not been

structurally distinguished one from the other based upon the combination of claim limitations now recited. The rejection is maintained for reasons of record.

Conclusion

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Pat. 5,925,546 (Pizza) is cited to show a mutant cholera toxin.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
March 28, 2005

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SUPERVISORY PATENT EXAMINER
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